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ON THE REACTION OF TISSUES TOWARDS SYNGENESIO-HOMOIO- AND HETEROTOXINS, AND ON THE POWER OF TISSUES TO DISCERN BETWEEN DIFFERENT DEGREES OF FAMILY RELATIONSHIP

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In a series of papers our collaborators and ourselves have analyzed the action of tissues upon each other after transplantation carried out under varied conditions. We wish now to suggest certain general conclusions of wider significance which may be drawn from the facts which have been previously published by us or which will be published in the near future. No attempt will be made here to review the facts on which our conclusions are based and we must refer instead to our papers.[1]

In 1907 we first noticed that lymphocytes may appear around or in transplanted tissue. Subsequently we observed this occurrence in various tissues after transplantation. We thought it possible that the action of lymphocytes depended upon the relationship between host and transplant. This was confirmed by our experiments.

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[1] Leo Loeb, *Archiv. f. Entwickelungsmech.*, 1897, VI, 1; 1907, XXIV, 638; 1911, XXXI, 456; 1898, VI, 297.

Leo Loeb and W. H. F. Addison, *Archiv. f. Entwickelungsmech.*, 1909, XXII, 73; 1911, XXXI, 44.

Llewellyn Sale, *Ibid.*, 1913, XXXVII, 248.

M. G. Seelig, *Ibid.*, 1913, XXXVII, 259.

Max W. Myer, *Ibid.*, 1913, XXXVIII, 1.

Cora Hesselberg, *Journ. Exp. Med.*, 1915, XXI, 164.

Cora Hesselberg, William Kerwin and Leo Loeb, *J. Med. Research*, 1918, XXXVIII, 17.

Leo Loeb, *Journ. Am. Med. Asso.*, 1915, LXIV, 726.

Leo Loeb, *Journ. Med. Research*, 1918, XXXVIII, 393; 1918, XXXIX, 189; 1918, XXXIX, 39; 1918, XXXIX, 71; 1918, XXXII, 353.

We found, however, that not only the lymphocytes, but also the blood and lymph vessels and fibroblasts behaved in a specific manner in accordance with the relationship between host and graft.

We assume that all the tissues of an individual have in common a certain chemical group which may be designated as individuality-differential. After transplanting a piece of an organ into a near relative of the donor of the tissue (syngenesiotransplantation), or into an unrelated individual of the same species (homoiotransplantation), or into an individual belonging to a different species (heterotransplantation), the individuality-differential is no longer adapted to its environment and acts as a syngenesio-, homoio-, heterodifferential, respectively. In this inadequate environment the individuality-differential assumes injurious properties, either directly or after interaction with the body fluids, some protein constituent of which contains likewise the individuality-differential or rather a group specifically combining with the individuality differential. It is probable that the second alternative represents the usual way in which the individuality-differential becomes a syngenesio-, homoio-, heterotoxin.

In certain cases the toxic character of the substance which originates after homoiotransplantation is strong enough to exert a direct injurious action on certain transplantation is strong enough to exert a direct injurious action on certain transplanted tissues, for instance, myxoid connective tissue and unstriated muscle. It can also directly interfere with those metabolic processes which lead to the production of epithelial pigment. In other cases, however, the toxic substances, while strong enough to modify the metabolism of the tissues, do not endanger the life of the transplant. This occurs after transplantation of glandular structures like kidney or thyroid or epithelial structures in general. But secondarily this change in the metabolism of the transplanted tissue alters the reaction of the host cells towards the graft. The lymphocytes are attracted, the vascular supply is diminished; fibroblasts are given freer access to the transplant, and moreover, the fibroblasts undergo secondary changes; they form fibrous tissue, while after autotransplantation the cytoplasm usually remains to a much greater extent intact without undergoing the secondary changes in contact with the grafted cells.

These toxic substances not only interfere with those proliferative processes which are of a regenerative character in the more restricted sense, but also with others caused by growth substances; thus they interfere with the production of experimental deciduomata in the uterus or with compensatory hypertrophy of the thyroid after homoiotransplantation, without however necessarily preventing these growth processes entirely. Ultimately they endanger the life of the exposed tissues, usually indirectly through the action of the lymphocytes and connective tissue cells, more rarely directly.

Furthermore the syngenesio-, homoio- and hetero-differentials may act secondarily as antigens directly or after interaction with the body fluids and then call forth the production of immune substances. Such immune substances however in most cases become demonstrable only if the strangeness of the antigen used has been very marked; this is for instance the case if a hetero-differential serves as an antigen (Schoene, M. S. Fleisher). A homoio-differential is only in some cases able to become an antigen. Under certain conditions homoio-haemolysins can appear (Ehrlich and Morgenroth) or haemagglutinins (von Dungern and Hirschfeld) and furthermore homoio-immune substances can be produced against growing tumors and embryonal tissues (Fichera, Peyton Rous). In the case of tumor immunity lymphocytes play a very prominent part. This has been noted by a number of investigators. More recently the significance of lymphocytes in immunity has been demonstrated in varied experiments especially by J. B. Murphy and his collaborators. However, as we shall see presently, the direct reaction of tissues (including lymphocytes) against syngenesio-, homoio- and heterotoxins is a finer biochemical reaction than any reaction known so far and more delicate than the immune reactions.

These substances which function as individuality-differentials are produced in the active metabolism of cells; they can be demonstrated through their reaction after transplantation of metabolically active tissue, but not after transplantation of erythrocytes contained in a blood clot. The syngenesiotoxins are least toxic. Usually they call forth a lymphocytic reaction only slowly; but ultimately the lymphocytes appear even here and invade and destroy the strange tissue. At a time when the vascular and fibroblastic reactions should occur, the toxins may as yet be so weak that these two kinds of tissues may behave normally. In other cases, however, even the syngenesiotoxins may be strong enough to call forth an altered reaction of vessels and fibroblasts; the vessels may fail to be present in a large number by the graft and the fibroblasts may produce more fibrous tissue. This occurs typically in response to homoiotoxins; furthermore, in the presence of homoiotoxins lymphocytes appear early and in large masses. They, as well as the fibroblasts, may invade and destroy the strange tissue. In the case of the heterotoxins the direct injurious effect of the body fluids is much more pronounced, and in a general way this effect is the greater, the more distant the relationship between host and graft, but in this case also the cellular reactions of the host may secondarily contribute to the destruction of the strange tissues. The fibroblasts of the host have a tendency to form dense fibrous tissue around the graft and the blood and lymph vessels are usually extremely sparse in the direct neighborhood and in the interior of a heterograft; apparently the strange cells do not exert an attracting or stimulating influence on the growth of capillaries. While thus in these two respects the heterotoxins produce an effect which might have been foreseen from a study of homoiotoxins, the behavior of the lymphocytes seems to be different from what might have been expected. Instead of being attacked by lymphocytes even more actively than the homoio-tissues, the lymphocytic reaction is on the contrary decidedly weaker in the case of tissues of other species. Lymphocytes do not usually invade and destroy the tissue of a foreign species, although they may collect in a considerable number in the neighborhood of the graft and may occasionally invade it here and there in small areas and destroy these. They may appear in large quantities after the graft has been destroyed. This relative inactivity of the lymphocytes is surprising, if we consider the much greater strangeness between graft and host which results from heterotransplantation. But it may be just on account of the great strength of the heterotoxins that the reaction is weakened. We have seen above that the development of the specifically attracting substances depends upon the active metabolism of the graft as evidenced by the failure of the erythrocytes to attract the lymphocytes. In the case of heterotransplantation the action of the toxins may be so strong that it interferes with these specific metabolic activities of the transplanted cells, and thus the reaction would naturally become weaker. It may also be that the scarcity of vessels around and in the graft may contribute to this result, these vessels acting as the channels through which the lymphocytes reach the graft. But that this factor can not be the only reason is clear from a study of certain areas of the transplant occasionally found in which the blood vessel supply may be somewhat better, but in which, nevertheless, the lymphocytic infiltration of the graft is absent or slight.

There is then a graded reaction of various tissues of the host towards transplants. At one end of the series we find the autotransplants; these are followed by the various kinds of syngenesio-, by homoio- and heterotransplants. Autotransplants call forth a marked vascular reaction. This reaction decreases in the direction towards heterotoxins; it is already very weak in most cases of homoiotoxins. The fibroblasts remain relatively well preserved, form least fibrillar material and tend to the production of myxoid tissue under the influence of those conditions which prevail in the case of autotransplantation. Here they are prevented at most places from breaking into the glandular structures; in the presence of homoio- and hetero- and even of syngenesio-toxins they tend in a higher degree towards the production of fibrillæ. Lymphocytes are attracted by syngenesiotoxins and still more by homoiotoxins; here a maximum is reached. A decrease occurs again in the region of the heterotoxins. The number of fibroblasts invading the glandular transplant is likewise greatest in the case of homoiotransplantation. Again a decrease seems to occur in the case of heterotransplants.

We may express these facts also in a somewhat different way. Under conditions of autotransplantation the tissues give off substances which correspond to the identity of the individuality-differentials in the host and graft. These substances, which may be designated as "auto-substances," stimulate directly or indirectly the vascular supply of the tissues belonging to the same individual. And they also exert directly or indirectly a definite effect upon the fibroblasts, keeping them active and preventing them from undergoing those processes which probably represent a decline in normal metabolism and which lead to the production of fibrous tissue at the expense of the healthy active cytoplasm. In the absence of these auto-substances, the vascular supply is lessened in direct proportion to the greater distance of the relationship between host and graft. To a certain extent syngenesiotoxins still take the place of the auto-substances characteristic of the interaction between the own tissues and body fluids. Some syngenesiotoxins however can do so only to a very slight extent; homoiotoxins are still less able to take the place of auto-substances and least of all heterotoxins. In the case of homoio- and heterodifferentials the stimulating effect of the "auto substances" is lacking; they behave in certain respects like foreign bodies.

On the other hand the autosubstances exert no attracting influence on the lymphocytes, while the syngenesiotoxins exert at first a very slight, but gradually cumulative, effect; the homoiotoxins exert the maximum effect; and then a decrease again takes place in the region of the heterodifferentials.

It might be suggested that the same auto-substances play a part in the interaction between the normal tissues of an individual. It is quite evident that the effect of the autosubstances would be beneficial to the tissues and contribute to their nourishment. Thus the body would possess a system of very finely acting chemical autoregulators which keep the vascular supply at the point of greatest intensity and prevent the fibroblasts from forming dense fibrous tissue which again would interfere with the nourishment of the tissues and which insure such an interaction of tissues that the normal structure results. Strange tissues do not exhibit the effect of such autosubstances, even if such strange tissues should temporarily multiply mitotically, and therefore they perish in the end.

On the other hand, autosubstances are indifferent, as far as the lymphocytes are concerned, while syngenesio- and homoio- and to some extent heterotoxins attract them. The lymphocytes as well as invading fibroblasts, are a destructive element and the effect of both is eliminated through the action of autosubstances; again a beneficial adaptation. Hypothetically we might thus explain in part at least the changes of tissues in old age. The effect of the autosubstances would be strongest in young individuals and decrease in the less actively metabolizing older tissues; and here we find, therefore, changes which are characteristic of a decrease in the autosubstances, or rather of specific metabolic substances which have the "auto" character and at the same time are characteristic of the specific organ activity. Therefore in old age the fibroblasts around the parenchyma from fibrous tissue and the vascular supply decreases. In the embryo we find least fibrous and most myxoid tissue and the best vascular supply.

Correspondingly we find least dense fibrous tissue around actively metabolizing parenchyma, while around the metabolically less active excretory ducts there is usually a coat of much more dense fibrous tissue. Thus it might be tentatively suggested that a decrease in these autosubstances, to the existence of which the results of tissue transplantation point, is at least partially responsible for the changes which take place in old age. Other factors of a different nature play certainly a part. Thus the corpus luteum stimulates the activity of the uterine connective tissue and epithelium. In later periods of life this stimulating influence is lacking.

While the autosubstances increase directly or indirectly the vascular supply, they very effectively limit the growth of fibroblasts in contact with epithelial elements. We have previously shown through transplantation experiments that during regeneration the epithelium limits the growth of the connective tissue.[2] In a similar way perhaps the endothelium of the blood vessels limits the growth of the connective tissue. Our further experiments lead to the conclusion that this restraining influence exerted by endothelium and epithelium upon connective tissue migration and proliferation is a specific effect. The auto-substances possess it in the highest degree. It is less marked in the case of syngenesio- and still less in the case of homoiotoxins. But even the hetero-substances still exert a certain restraining influence, at least temporarily on the connective tissue and they are thus in this respect more effective than foreign bodies. It is again clear that considering the tendency of fibroblasts and lymphocytes to migrate actively into parenchyma and to destroy it, the epithelial structures can be assured of preservation only, if the auto-substances possess some kind of a restraining influence on the connective tissue.

It is probable that not only in old age but also under certain pathological conditions, the activity of these autosubstances is interfered with, and that thus cirrhotic processes may be produced in various parenchymatous organs. The usual assumption is that all these fibrous changes are the result of an actual destruction of the epithelium, that they are therefore due to regeneration in the more restricted sense of the term. It is probable that both these processes may occur in different cases.

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[2] Leo Loeb, *Arch. f. Entwickelungsmech.*, 1898, VI, 297 (p. 319).

As we have shown, various tissues, but particularly the lymphocytes, are able to distinguish not only between tissues belonging to the same and other individuals of the same species, but even to recognize the difference in degree of relationship. They behave in a graded manner towards their own tissues, the tissues of a brother, mother, the tissues of a not related individual of the same species and the tissues of an individual of a different species. These reactions must be in response to specific substances given off by these tissues, the autosubstances, the syngenesio-, homoio- and heterotoxins. Whether these substances are identical with the individuality-differentials residing in the tissues or whether they are due to an interaction between the individuality-differentials residing in the tissues and adapted substances in the body fluids can not be decided definitely at present; however, the latter assumption seems to be more probable. These responses represent to our knowledge the finest biochemical reactions which are known at the present time and surpass even the immune reactions which permit us to distinguish only between different species and in a few cases only between individuals of the same species.[3]

These reactions we may hope will contribute to an understanding of the behavior and the functions of tissues in general as distinct from the specific functions of organs which under certain conditions are added to these more general tissue reactions, and thus they may contribute to a physiology of tissues as contrasted with the physiology of organs. Further experiments will have to determine, how far the effect of the parenchyma on the fibroblasts and blood vessels is a direct one and how far secondary interactions between fibroblasts and blood vessels enter into these reactions.

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[3] It is possible that a further development of the immunological methods used by von Dungern and Hirschfeld and by Todd and White (*Proc. Royal Soc.*, 1910, LXXXII, 416) will also lead to a differentiation in the relationship of individuals of the same species.

These various substances (autosubstances, syngenesio-, homoio- heterodifferentials) have in addition to the functions which concern the effect of cells upon each other added functions of a specific nature. This is indicated by the existence of specifically adapted substances like the tissue coagulins which determine in a specifically adapted manner the coagulation of the blood of various species.[4]

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[4] Leo Loeb, *Montreal Med. Journal,* July, 1903; *Virchow Archiv,* 1904, CLXXVI, 10; *Biochem. Zeitschrift,* 1910, XXVIII, 169.